Exhibit B

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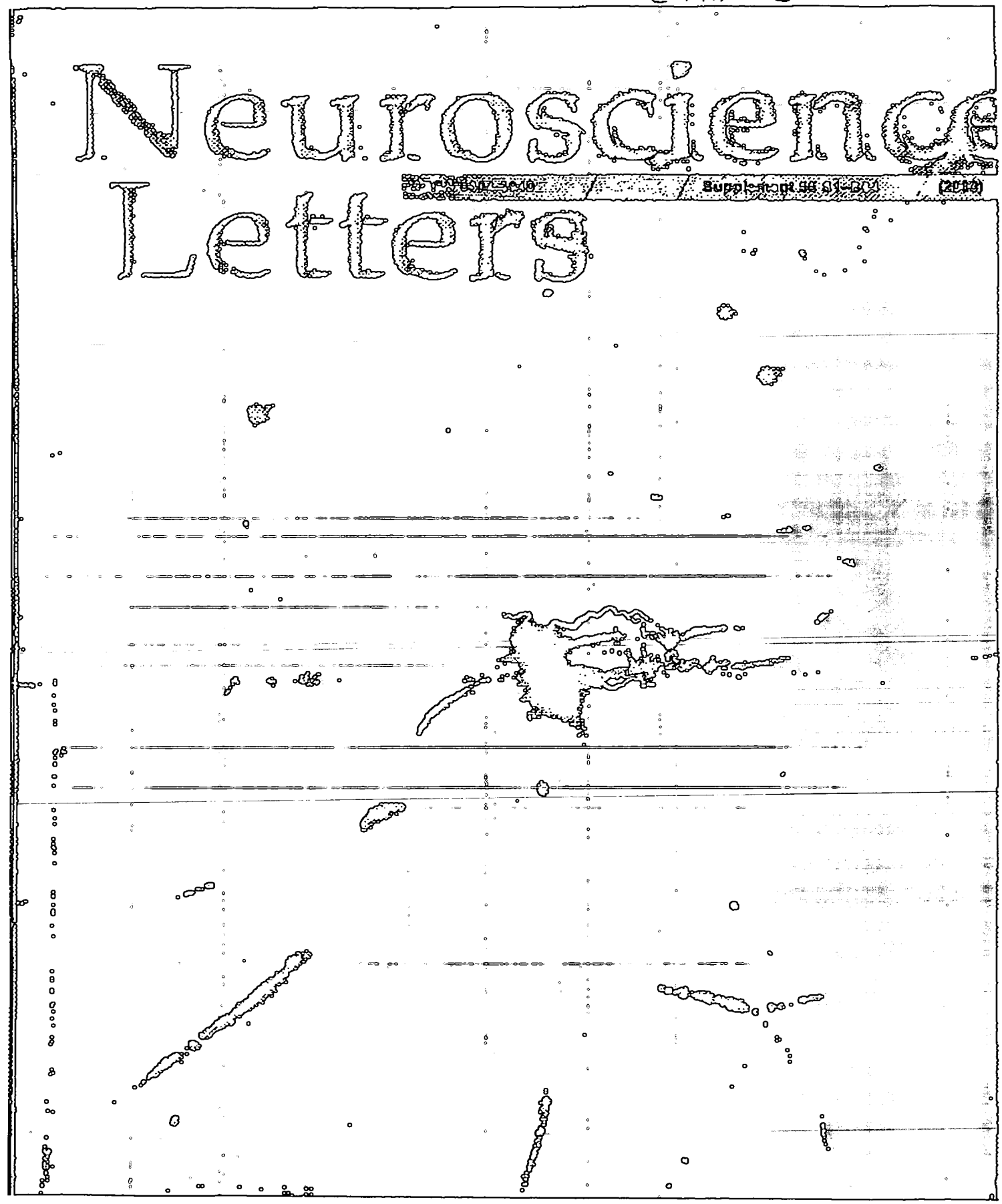

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SUPPLEMENT

ABSTRACTS OF THE NINTH MEETING OF THE ISRAEL SOCIETY FOR NEUROSCIENCES

Eilat, Israel, December 3 – 6, 2000

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one the V726A mutation. The frequency of each mutation was similar in the healthy North-African Jewish cohort. The group of carriers among the North-African (8 of 22) or Iraqi Jewish (7 of 23) relapsing remitting MS patients had a shorter time to reach EDSS 3 and EDSS 6 than non-carriers. Median times in the combined group of carriers were 1 year to reach EDSS 3 and 6 years to reach EDSS 6. In the non-carriers the median EDSS times were 10 years to reach EDSS 3 (p=0.0007) and 23 years to reach EDSS 6 (p 0.0047). While the results confirm that MEFV mutations do not confer susceptibility to develop MS, they indicate an association between MEFV mutations and an increased risk for rapid development of disability in Sephardi Jews.

PROTECTIVE EFFECTS OF TV3326 AGAINST NEURONAL DAMAGE AND SPATIAL MEMORY DEFICITS INDUCED IN RATS BY INTRACEREBROVENTRICULAR INJECTION OF STREPTOZOTOCIN

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TV3326, (N-propargyl-(3R)-aminoindan-5-yl-ethyl,methyl carbamate) was synthesized to combine the neuroprotective properties of rasagiline, with those of the cholinesterase inhibitor, rivastigmine. Intracerebroventricular (icv) injection of streptozotocin (STZ) reduces glucose utilization in the cortex and ChAT in the hippocampus and has been suggested as a model for Alzheimer's disease (AD). The present study evaluated the effect of TV3326 on morphological changes and spatial memory deficits induced by icv STZ. Male rats, aged 3 months were given 1-3 unilateral icv injections of STZ, 1.5 mg or 3 bilateral injections of 0.25mg STZ. Control rats received artificial cerebrospinal fluid. After 6 weeks, rats were anesthetized and brains fixed by transcardial perfusion with paraformaldehyde. Neurodegeneration was assessed by silver impregnation, and gliosis by immunohistochemical detection of complement receptor 3. STZ produced shrinkage and axonal degeneration in the anterior hippocampus and adjacent fornix, and microgliosis in the periventricular corpus callosum and fornix. STZ also induced a uniform orientation of microglial fibers in the periventricular zone, whereas in controls, orientation varied in individual microglia. Bilateral injection of STZ caused a marked impairment in spatial memory measured 3 weeks after the last injection. TV3326 (2.5 μmole/kg) given by gastric gavage, once daily for 3 weeks, at the time of STZ administration, reduced damage in the dorsal fornix and normalized orientation of microglial fibers, and almost completely prevented the memory deficits seen after the bilateral injection of STZ. Given the evidence for involvement of reactive microglia in human AD, TV3326 could provide some neuroprotection for AD patients.

TRANSGENIC ACETYLCHOLINESTERASE OVER-EXPRESSION INCREASES WEIGHT LOSS RESPONSE TO DIETARY RESTRICTION

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Although human anorexia nervosa (AN) typically begins with restriction of food intake, most people who engage in voluntary diet restriction do not develop AN. Since there is strong evidence for a genetic contribution to human AN, we searched for brain-expressed regulatory genes that could potentially control the response to diet restriction (DR). Transgenic overexpression of human synaptic acetylcholinesterase (AChE-S) was associated with significant increases in mean body weight of FVB/N mice, suggesting an alteration in body weight regulation. To test this hypothesis, control FVB/N and transgenic female mice, after reaching a uniform baseline body weight at 6-7 weeks of age, were assigned to ad libitum (AL), or DR to 60% or 50% of AL food intake respectively, for 6 weeks. AChE-S transgenic mice lost weight significantly more rapidly than FVB/N controls. This was associated with differences in some physiological responses to DR. Diet restricted control FVB/N mice lowered their body temperature, conserving energy through reduced heat production unlike diet restricted transgenic animals which suffer impaired control over body temperature due to excess acetylcholinesterase. Moreover, transgenic mice increased locomotor activity in response to DR more than did FVB/N mice. These findings constitute the first report that inherited excess of acetylcholinesterase can affect body weight and temperature regulation in response to food restriction. AChE-S transgenic mice may thus constitute an important model for understanding the behavioral physiology associated with starvation as in human AN.

TYROSINE NUTRITIONAL SUPPLEMENTATION: EFFECTS ON BEHAVIOR IN DIET RESTRICTED FEMALE C57BL MICE.

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There is evidence for reduced norepinephrine (NE) metabolism in human anorexia nervosa (AN) as well as in rodent diet restriction (DR). Since NE modulates cognitive and emotional behavior, we examined effects of the amino acid L-tyrosine (TYR), from which NE is synthesized. Ad libitum (AL) food intake was assessed in female C57BL mice, 6-7 weeks of age. Next, for some mice, the diet was gradually reduced to 70% and to 50% of daily AL intake, while control mice continued with AL feeding. Then some DR mice received a synthetic amino acid diet (AAD controls) whereas the other DR mice received additional TYR. The estimated daily TYR intake was 18 mg for AL controls, 13mg for DR70%, 9mg for DR50% and 57mg for TYR supplemented DR mice. Mice were tested in the elevated plus maze, in which two opposite arms are partially enclosed by vertical walls whereas the other two arms are open. DR increased time spent in the open arms without affecting motor activity. TYR supplementation increased motor activity in the enclosed arms and reduced time spent in the open arms to AL control levels. This latter effect, combined with our earlier findings, suggests that while DR reduces fear-induced behavioral inhibition, TYR normalizes behavioral inhibition without a change in body weight. Since TYR is a normal constituent of diet, with adjustment of TYR intake, this may lead to treatment of the cognitive and emotional aspects of long-term starvation as in human AN.

EFFECT OF IGF-1 AND HEXARELIN ON DOPAMINE INDUCED TOXICITY IN NEUROBLASTOMA AND GLIOMA. EVIDENCE FOR P53 MEDIATION

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Insulin like growth-factor-1 (IGF-1), possesses a marked neurotrophic activity. Hexarelin, a growth-hormone secretagogue peptide was found to stimulate IGF-1 secretion, and to activate certain neurons in the brain. We studied the effect of IGF-1 and Hexarelin on dopamine (DA) induced toxicity in human neuroblastoma (SK-N-SH), in rat glioma (C6), and in primary brain culture. We found, in rat cerebellar culture, that IGF-1 (0.5 μg/ml) suppressed cell death induced by DA (0.1mM) after 2 and 4 days of incubation ($p < 0.05$), in neuroblastoma and in glioma cells. DA induced a dose dependent toxicity which was antagonized (only neuroblastoma) by IGF-1 (0.5 μg/ml). Hexarelin (0.1-100 μM) stimulated basal cell viability (120-160%) in both cell-lines, however the peptide did not protect cells of the two cultures from death induced by exposure to serum deficiency and to DA. Moreover IGF-1 partially antagonized the DA-induced apoptosis evidenced by flowcytometry in the neuroblastoma cells. Using western blot analysis, we found in neuroblastoma and in glioma cells, that DA (125 and 250μM) decreased markedly the expression of P53 mutant protein, and this effect was reversed in neuroblastoma by IGF-1. Cycloheximide IGF-1 protects neurons but not glial cells against DA toxicity. Hexarelin stimulates survival of both cell-lines, but does not protect cells against DA toxicity. DA toxicity is accompanies by a significant decrease in the expression of P53 mutant protein, an effect antagonized by IGF-1 in neurons. We suggest that IGF-1 is an important neuroprotective agent against DA neurotoxicity, and may play a role in Parkinson's disease.

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